REMARKS

After entry of this amendment, claims 2-15, 23, 28, 31-33, and 50-65 are pending. Claim 1 has been cancelled without prejudice or disclaimer. Claim 2 has been amended without prejudice or disclaimer and finds support *inter alia* in the original claims. Further support is found in the specification at page 7, lines 5-12, page 12, lines 23-28, and page 23, lines 1-22. No new matter has been added.

Claim Rejections – 35 U.S.C. § 112, First Paragraph

Claims 1-15, 23, 28, 31-33, and 50-65 are rejected under 35 U.S.C. § 112, first paragraph, based on the specification allegedly not enabling a person skilled in the art to make and/or use the invention commensurate in scope with the claims. The Examiner reasons that, although the specification is enabled for a process for production of pantothenate comprising culturing a *Bacillus subtilis* host cell transformed with the plasmid pAN396 containing the *glyA* gene consisting of SEQ ID NO: 24 and the plasmid pAN824 containing the *serA* gene consisting of SEQ ID NO: 31, the specification does not reasonably provide enablement for any other embodiment as recited in the claims. To support this position, the Examiner further argues that the art is unpredictable and the amount of guidance provided in the specification is limited, and thus, undue experimentation would be required to practice the present invention. Applicants respectfully disagree and submit that the claims, as amended, are enabled in view of the factual factors identified as relevant in *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988).

1. Nature of the Invention / Breadth of the Claims

The nature of the present invention is related to a biotechnological process for the production of pantothenate with the aid of recombinant microorganisms. The claims are drawn to a process for the enhanced production of pantothenate comprising culturing a recombinant microorganism having a deregulated pantothenate biosynthetic pathway and a deregulated methylentetrahydrofolate (MTF) biosynthetic pathway, wherein the deregulation of the MTF biosynthetic pathway is achieved by overexpressing a gene selected from the group consisting of *gcv*, *serA*, *serC*, *serB*, *glyA*, *sul*, *fol*, *mtrA*, *pab*, *panB* or *purR*, wherein aforementioned genes are derived from a microorganism of the genera *Bacillus*, *Corynebacterium*, *Lactobacillus*,

Lactococci or *Streptomyces*. Thus, the claims as amended are more commensurate with the supporting disclosure.

2. State of the Art

The Examiner did not specifically address the factor concerning the state of the art. However, it is noted that the use of microorganisms for the production of pantothenate is known in the art. For instance, in U.S. Pat. Nos. 5,932,457 and 6,184,006, microorganisms from the genera of *Escherichia*, *Arthrobacter*, *Corynebacterium*, *Brevibacterium* and yeast are disclosed for the production of pantothenate using different enzymes of the pantothenate biochemical pathway. Thus, the state of the art is such that expressing an enzyme in a microorganism is well within the ordinary skill of the art.

Moreover, as evidenced by the enclosed excerpt from the biochemistry textbook by Voet et al. (Biochemistry, Second Edition, 1995, John Wiley & Sons, Inc., pp. 761-764, particularly Figure 24-39 at page 763), the MTF (methylen-THF) biosynthetic pathway is well known to those skilled in the art. What was not known and discovered by the inventors of the present application is the important involvement and contribution of the MTF biosynthetic pathway in the production of pantothenic acid. Since expressing an enzyme in a microorganism is within the ordinary skill of the art as discussed above, expression of genes involved in the MTF biosynthetic pathway for the purpose of enhancing the production of pantothenate would not require undue experimentation.

3. Skill of Those in The Art

The Examiner also did not specifically address the factor concerning the skill of those in the art, but it is certainly high. Judging from the references noted above, a person of ordinary skill in the art involved in the recombinant production of pantothenate would have an advanced degree (likely a Ph.D.) in the molecular biological science and several years of work experience. Such an artisan would be highly trained in using various recombinant DNA systems. Such a highly trained scientist would also have a familiarity with overexpressing genes in different microorganisms, particularly in light of the technical teaching provided in the specification and available in the art. The very high training and experience level of those skilled in this art means

that only very extensive and very unpredictable experimentation would rise to the level of "undue" in this art.

4. Predictability of the Art / Guidance

The Examiner asserts that an in-depth understanding structure/function relationship is required for enzyme modification and directed evolution techniques available in the art are useful only for searching and screening for enzymes with a desired property. The Examiner refers to Chica et al. (Curr. Opin. Biotechnol., 2005, hereinafter "Chica") and Sen et al. (Appl. Biochem. Biotechnol., 2007, hereinafter "Sen") for support. Applicants respectfully disagree.

As the Examiner correctly pointed out, Chica teaches the complexity of the structure/function relationship in enzymes and Sen teaches a method for the modification and design of enzymes to manipulate the enzymatic activity and to increase the enantioselectivity. However, the claims are drawn to a process for the production of pantothenate by overexpressing genes involved in the MTF biosynthetic pathway, not the discovery of new genes or gene functions *per se*. Moreover, the claims as amended recite overexpression and not any type of deregulation.

Furthermore, as discussed above, expressing an enzyme in a microorganism is well within the ordinary skill of the art. Once a gene or genes are identified as being important for a particular purpose, a skilled artisan would be able to overexpress such a gene or genes in a desired microorganism. Microorganisms such as *Bacillus*, *Escherichia*, *Corynebacterium*, and *Lactobacillus* are routinely used for genetic engineering purpose, which means that the predictability of using those microorganisms in overexpressing a desired gene is relatively high.

Additionally, as discussed in the Response dated January 29, 2009, the specification, by way of working examples, shows that the claimed process results in the enhanced production of pantothenate by culturing a *Bacillus* host cell transformed with a *panB* gene (Example I), a *glyA* gene (Example III), a *serA* gene (Example IV), and a disrupted *purR* gene (Example VI). Additionally, the specification further provides detailed guidance as to the expression of genes in a microorganism such as promoter sequences (page 20, lines 1-27), artificial ribosome binding sites (page 21, lines 2-31), and antibiotic resistance sequences (page 22, lines 10-24). Guidance as to constructing vectors for overexpressing genes in microorganisms such as *Escherichia coli*

is also available in the art and routinely used by a skilled artisan. A well known example is the textbook by Sambrook et al. entitled "Molecular Cloning." Accordingly, Applicants believe that the application as filed contains sufficient guidance and direction to enable a skilled artisan to practice the claimed invention.

5. The Presence of Working Examples / Experimentation Required

While working examples demonstrating the overexpression of a *panB* gene (Example I), a *glyA* gene (Example III), a *serA* gene (Example IV), and a disrupted *purR* gene (Example VI) in *Bacillus* are provided in the specification, the Examiner asserts that these working examples fail to enable the full scope of the claimed process. Applicants disagree.

As discussed above, the knowledge regarding recombinantly expressing an enzyme in a microorganism and the MTF biosynthetic pathway is fully available to one skilled in the pertinent art at the time of the invention. Furthermore, the specification provides detailed guidance on how to isolate a gene involving in MTF biosynthetic pathway, how to generate an expression cassette containing such a gene, how to transform the expression cassette into a microorganism, and how to detect the effect of the transgene expression on pantothenate production. See e.g., Examples I and III-VI. Additionally, screening recombinant microorganisms for enhanced production of pantothenate is routine and not undue experimentation. Because of the detailed guidance provided in the specification and the knowledge of the art, it is respectfully submitted that no undue experimentation would be required for one skilled artisan to make and use the claimed process as amended with the genes that are not exemplified in the specification. As stated in *Ex parte Jackson*, under the applicable law, the test for "undue experimentation" is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 USPQ 804, 807 (1982). On the facts of this case, the detailed guidance provided in the specification and the routine nature of the experimentation required for making and using the claimed process as amended weight in favor of finding enablement.

6. Summary of *Wands* Factors

In view of the detailed description, guidance, working examples, state and knowledge of the art, and high level of skill, the specification enables the full scope of the claims without undue experimentation. On these facts, a proper analysis of the relevant factors supports a finding of enablement. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above remarks and further in view of the above amendments, Applicants respectfully request withdrawal of the rejections and allowance of the claims. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the number given below.

Accompanying this response is a petition for a one-month extension of time to respond to the Office Action mailed April 28, 2009 with the required fee. No further fees are believed due. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 13311-00036-US from which the undersigned is authorized to draw.

Respectfully submitted,

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Attachement: Voet et al., Biochemistry, Second Edition, 1995, John Wiley & Sons, Inc., pp. 736, 761-764, and 826.